HYDROXYUREA- hydroxyurea capsule
AvKARE, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
Hydroxyurea Capsules USP

Rx Only

These highlights do not include all the information needed to use HYDROXYUREA CAPSULES safely and effectively. See full prescribing information for HYDROXYUREA CAPSULES.

HYDROXYUREA capsules, for oral use

Initial U.S. Approval: 1967

INDICATIONS AND USAGE

Hydroxyurea capsules are an antimetabolite indicated for the treatment of:

- Resistant chronic myeloid leukemia. (1)
- Locally advanced squamous cell carcinomas of the head and neck, (excluding lip) in combination with concurrent chemoradiation. (1)

DOSAGE AND ADMINISTRATION

- Individualize treatment based on tumor type, disease state, response to treatment, patient risk factors, and current clinical practice standards. (2.1)
- Renal impairment: Reduce the dose of hydroxyurea capsules by 50% in patients with creatinine clearance less than 60 mL/min. (2.3, 8.6, 12.3)

DOSAGE FORMS AND STRENGTHS

- Capsules: 500 mg (3)

CONTRAINDICATIONS

- In patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation. (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression: Do not give if bone marrow function is markedly depressed. Monitor hematology labs and interrupt, reduce dose as appropriate. (5.1)
- Malignancies: Advise protection from sun exposure and monitor for secondary malignancies. (5.2)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.3, 8.1, 8.3)
- Vasculitic toxicities: Discontinue hydroxyurea and initiate treatment if this occurs. (5.4)
- Live Vaccinations: Avoid live vaccine use in a patient taking hydroxyurea capsules. (5.5)
- Risks with concomitant use of antiretroviral drugs: Pancreatitis, hepatotoxicity, and neuropathy have occurred. Monitor for signs and symptoms in patients with HIV infection using antiretroviral drugs; discontinue hydroxyurea capsules, and implement treatment. (5.6)
- Radiation recall: Monitor for skin erythema in patients who previously received radiation and manage symptomatically. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (≥30%) are hematological, gastrointestinal symptoms, and anorexia. (6)
To report SUSPECTED ADVERSE REACTIONS, contact AvKARE, Inc. at 1-855-361-3993; email drugsafety@avkare.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Antiretroviral drugs (7.1) (7)
• Laboratory Test Interference (7.2) (7)

USE IN SPECIFIC POPULATIONS

- *Lactation* Hydroxyurea is excreted in human milk. Discontinue breastfeeding during treatment with hydroxyurea capsules. (8.2)
- *Geriatric Use* Care should be taken in dose selection and may require a lower dose regimen and monitoring of renal

function. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Hydroxyurea capsules are indicated for the treatment of:

- Resistant chronic myeloid leukemia.
- Locally advanced squamous cell carcinomas of the head and neck (excluding the lip) in combination with chemoradiation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

Hydroxyurea capsules are used alone or in conjunction with other antitumor agents or radiation therapy to treat neoplastic diseases. Individualize treatment based on tumor type, disease state, response to treatment, patient risk factors, and current clinical practice standards.

Base all dosage on the patient's actual or ideal weight, whichever is less.

Hydroxyurea capsules are a cytotoxic drug. Follow applicable special handling and disposal procedures [*see References (15)*].

Patients should swallow hydroxyurea capsules whole and not to open, since hydroxyurea is a cytotoxic drug.

Prophylactic administration of folic acid is recommended *[see Warnings and Precautions (5.7)]*.

2.2 Dose Modifications for Toxicity

Monitor for the following and reduce the dose or discontinue hydroxyurea capsules accordingly:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Cutaneous vasculitis *[see Warnings and Precautions (5.4)]*

Monitor blood counts at least once a week during hydroxyurea therapy. Severe anemia must be corrected before initiating therapy with hydroxyurea capsules. Consider dose modifications for other toxicities.

2.3 Dose Modifications for Renal Impairment

Reduce the dose of hydroxyurea capsules by 50% in patients with measured creatinine clearance of less than 60 mL/min or with end-stage renal disease (ESRD) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]* .

Creatinine Clearance (mL/min)	Recommended Hydroxyurea Initial Dose (mg/kg once daily)
≥60	15
<60 or ESRD*	7.5

* On dialysis days, administer hydroxyurea capsules to patients following hemodialysis.

Close monitoring of hematologic parameters is advised in these patients.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 500 mg purple opaque cap and pink opaque body imprinted in black ink stylized barr 882.

4 CONTRAINDICATIONS

Hydroxyurea is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Hydroxyurea causes severe myelosuppression. Treatment with hydroxyurea should not be initiated if bone marrow function is markedly depressed. Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often and are seldom seen without a preceding leukopenia. Bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; use hydroxyurea cautiously in such patients.

Evaluate hematologic status prior to and during treatment with hydroxyurea capsules. Provide supportive care and modify dose or discontinue hydroxyurea capsules as needed. Recovery from myelosuppression is usually rapid when therapy is interrupted.

5.2 Malignancies

Hydroxyurea is a human carcinogen. In patients receiving long-term hydroxyurea for myeloproliferative disorders, secondary leukemia has been reported. Skin cancer has also been reported in patients receiving long-term hydroxyurea. Advise protection from sun exposure and monitor for the development of secondary malignancies.

5.3 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, hydroxyurea capsules can cause fetal harm when administered to a pregnant woman. Hydroxyurea was embryotoxic and teratogenic in rats and rabbits at doses 0.8 times and 0.3 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis. Advise pregnant women of the potential risk to a fetus *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during and after treatment with hydroxyurea capsules for at least 6 months after therapy. Advise males of reproductive potential to use effective contraception during and after treatment with hydroxyurea capsules for at least 1 year after therapy *[see Use in Specific Populations (8.1, 8.3)]*.

5.4 Vasculitic Toxicities

Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. If cutaneous vasculitic ulcers occur, institute treatment and discontinue hydroxyurea capsules.

5.5 Live Vaccinations

Avoid use of live vaccine in patients taking hydroxyurea capsules. Concomitant use of hydroxyurea capsules with a live virus vaccine may potentiate the replication of the virus and/or may increase the adverse reaction of the vaccine because normal defense mechanisms may be suppressed by hydroxyurea capsules. Vaccination with live vaccines in a patient receiving hydroxyurea capsules may result in severe infection. Patient’s antibody response to vaccines may be decreased. Consider consultation with a specialist.

5.6 Risks with Concomitant Use of Antiretroviral Drugs

Pancreatitis, hepatotoxicity, and peripheral neuropathy have occurred when hydroxyurea was administered concomitantly with antiretroviral drugs, including didanosine and stavudine *[see Drug Interactions (7.1)]* .

5.7 Radiation Recall

Patients who have received irradiation therapy in the past may have an exacerbation of post-irradiation erythema. Monitor for skin erythema in patients who previously received radiation and manage symptomatically.

5.8 Macrocytosis

Hydroxyurea may cause macrocytosis, which is self-limiting, and is often seen early in the course of treatment. The morphologic change resembles pernicious anemia, but is not related to vitamin B_{12} or folic acid deficiency. This may mask the diagnosis of pernicious anemia. Prophylactic administration of folic acid is recommended.

5.9 Laboratory Test Interference

Interference with Uric Acid, Urea, or Lactic Acid Assays is possible, rendering falsely elevated results of these in patients treated with hydroxyurea [see Drug Interactions (7.2)].

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other labeling sections:

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*
- Embryo-fetal toxicity *[see Warnings and Precautions (5.3)]*
- Vasculitic toxicities *[see Warnings and Precautions (5.4)]*
- Risks with concomitant use of antiretroviral drugs *[see Warnings and Precautions (5.6)]*
- Radiation recall *[see Warnings and Precautions (5.7)]*
- Macrocytosis *[see Warnings and Precautions (5.8)]*

6.1 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of hydroxyurea. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

- *Reproductive System and Breast disorders:* azoospermia, and oligospermia
- *Gastrointestinal disorders:* stomatitis, nausea, vomiting, diarrhea, and constipation
- *Metabolism and Nutrition disorders:* anorexia, tumor lysis syndrome
- *Skin and subcutaneous tissue disorders:* maculopapular rash, skin ulceration, dermatomyositis-like skin changes, peripheral and facial erythema, hyperpigmentation, nail hyperpigmentation, atrophy of skin and nails, scaling, violet papules, and alopecia
- *Renal and urinary disorders:* dysuria, elevations in serum uric acid, blood urea nitrogen (BUN), and creatinine levels
- *Nervous system disorders:* headache, dizziness, drowsiness, disorientation, hallucinations, and convulsions
- *General Disorders:* fever, chills, malaise, edema, and asthenia
- *Hepatobiliary disorders:* elevation of hepatic enzymes, cholestasis, and hepatitis
- *Respiratory disorders:* diffuse pulmonary infiltrates, dyspnea, and pulmonary fibrosis
- *Hypersensitivity:* Drug-induced fever (pyrexia) (>39°C, >102°F) requiring hospitalization has been reported concurrently with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary,

dermatological or cardiovascular manifestations. Onset typically occurred within 6 weeks of initiation and resolved upon discontinuation of hydroxyurea. Upon re-administration fever re-occurred typically within 24 hours.

Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea or radiation treatment alone. These effects primarily include bone marrow depression (anemia and leukopenia), gastric irritation, and mucositis. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (<100,000 cells/mm ^{3}) has occurred in the presence of marked leukopenia. Hydroxyurea may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

To report SUSPECTED ADVERSE REACTIONS contact AvKARE, Inc. at 1-855-361-3993; email drugsafety@avkare.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

7.1 Increased Toxicity with Concomitant Use of Antiretroviral Drugs

Pancreatitis

In patients with HIV infection during therapy with hydroxyurea and didanosine, with or without stavudine, fatal and nonfatal pancreatitis have occurred. Hydroxyurea is not indicated for the treatment of HIV infection; however, if patients with HIV infection are treated with hydroxyurea, and in particular, in combination with didanosine and/or stavudine, close monitoring for signs and symptoms of pancreatitis is recommended. Permanently discontinue therapy with hydroxyurea in patients who develop signs and symptoms of pancreatitis.

Hepatotoxicity

Hepatotoxicity and hepatic failure resulting in death have been reported during postmarketing surveillance in patients with HIV infection treated with hydroxyurea and other antiretroviral drugs. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. Avoid this combination.

Peripheral Neuropathy

Peripheral neuropathy, which was severe in some cases, has been reported in patients with HIV infection receiving hydroxyurea in combination with antiretroviral drugs, including didanosine, with or without stavudine.

7.2 Laboratory Test Interference

Interference with Uric Acid, Urea, or Lactic Acid Assays

Studies have shown that there is an analytical interference of hydroxyurea with the enzymes (urease, uricase, and lactate dehydrogenase) used in the determination of urea, uric acid, and lactic acid, rendering falsely elevated results of these in patients treated with hydroxyurea.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Hydroxyurea capsules can cause fetal harm based on findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]* . There are no data with hydroxyurea capsules use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration

of hydroxyurea to pregnant rats and rabbits during organogenesis produced embryotoxic and teratogenic effects at doses 0.8 times and 0.3 times, respectively, the maximum recommended human daily dose on a mg/m ^{2} basis *(see Data)*. Advise women of the potential risk to a fetus and to avoid becoming pregnant while being treated with hydroxyurea capsules.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs, and monkeys at doses within 1-fold of the human dose given on a mg/m ^{2} basis. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m ^{2} basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m ^{2} basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m ^{2} basis) to rats caused growth retardation and impaired learning ability.

8.2 Lactation

Risk Summary

Hydroxyurea is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed infant from hydroxyurea, including carcinogenicity, discontinue breastfeeding during treatment with hydroxyurea capsules.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating hydroxyurea therapy.

Contraception

Females

Hydroxyurea capsules can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during and after treatment with hydroxyurea capsules for at least 6 months after therapy. Advise females to immediately report pregnancy.

Males

Hydroxyurea may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during and after treatment with hydroxyurea capsules for at least 1 year after therapy *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on findings in animals and humans, male fertility may be compromised by treatment with hydroxyurea capsules. Azoospermia or oligospermia, sometimes reversible, has been observed in men. Inform male patients about the possibility of sperm conservation before the start of therapy *[see Adverse Reactions (6) and Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen. Hydroxyurea is excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.3)]* .

8.6 Renal Impairment

The exposure to hydroxyurea is higher in patients with creatinine clearance of less than 60 mL/min or in patients with end-stage renal disease (ESRD). Reduce dosage and closely monitor the hematologic parameters when hydroxyurea capsules are to be administered to these patients *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]* .

8.7 Hepatic Impairment

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

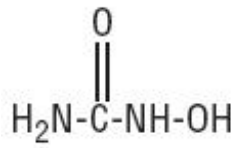
10 OVERDOSAGE

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages several times the therapeutic dose. Soreness, violet erythema, edema on palms and soles followed by scaling of hands and feet, severe generalized hyperpigmentation of the skin, and stomatitis have also been observed.

11 DESCRIPTION

Hydroxyurea Capsules USP are an antineoplastic available for oral use as capsules providing 500 mg hydroxyurea, USP. Inactive ingredients: anhydrous citric acid, benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, D&C red no. 28, D&C yellow no. 10 aluminum lake, dibasic sodium phosphate, edetate calcium disodium, FD&C blue no. 1, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40, FD&C red no. 40 aluminum lake, gelatin, lactose monohydrate, magnesium stearate, methylparaben, pharmaceutical glaze, propylparaben, propylene glycol, red iron oxide, sodium lauryl sulfate, sodium propionate, and titanium dioxide.

Hydroxyurea, USP is a white to off-white crystalline powder. It is hygroscopic and freely soluble in water, but practically insoluble in alcohol. Its structural formula is:



$CH_4N_2O_2$ M.W. 76.05

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various studies in tissue culture in rats and humans lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. *In vitro* studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radioresistant S-stage cells, and (2) holds other cells of the cell cycle in the G1 or pre-DNA synthesis stage where they are most susceptible to the effects of irradiation. The third mechanism of action has been theorized on the basis of *in vitro* studies of HeLa cells. It appears that hydroxyurea, by inhibition of DNA synthesis, hinders the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate; RNA and protein syntheses have shown no alteration.

12.3 Pharmacokinetics

Absorption

Following oral administration of hydroxyurea capsules, hydroxyurea reaches peak plasma concentrations in 1 to 4 hours. Mean peak plasma concentrations and AUCs increase more than proportionally with increase of dose.

There are no data on the effect of food on the absorption of hydroxyurea.

Distribution

Hydroxyurea distributes throughout the body with a volume of distribution approximating total body water.

Hydroxyurea concentrates in leukocytes and erythrocytes.

Metabolism

Up to 60% of an oral dose undergoes conversion through saturable hepatic metabolism and a minor pathway of degradation by urease found in intestinal bacteria.

Excretion

In patients with sickle cell anemia, the mean cumulative urinary recovery of hydroxyurea was about 40% of the administered dose.

Specific Populations

Renal Impairment

The effect of renal impairment on the pharmacokinetics of hydroxyurea was assessed in adult patients with sickle cell disease and renal impairment. Patients with normal renal function (creatinine clearance [CrCl] >80 mL/min), mild (CrCl 50 to 80 mL/min), moderate (CrCl = 30 to <50 mL/min), or severe (<30 mL/min) renal impairment received a single oral dose of 15 mg/kg hydroxyurea. Patients with ESRD received two doses of 15 mg/kg separated by 7 days; the first was given following a 4-hour hemodialysis session, the second prior to hemodialysis. The exposure to hydroxyurea (mean AUC) in patients with CrCl <60 mL/min and those with ESRD was 64% higher than in patients with normal renal function (CrCl >60 mL/min). Reduce the dose of hydroxyurea when it is administered to patients with creatinine clearance of <60 mL/min or with ESR *D following hemodialysis [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)]* .

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Conventional long-term studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. However, intraperitoneal administration of 125 to 250 mg/kg hydroxyurea (about 0.6 to 1.2 times the maximum recommended human oral daily dose on a mg/m ^{2} basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m ^{2} basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

15 REFERENCES

OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Hydroxyurea Capsules USP 500 mg are available as a two-piece hard gelatin capsule with purple opaque cap and pink opaque body filled with white powder, imprinted in black ink stylized **barr 882** and packaged in bottles of 100 capsules (NDC 42291-321-01).

16.2 Storage

Store at 20º to 25ºC (68º to 77ºF) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

STORE IN A DRY ATMOSPHERE AND AVOID EXCESSIVE HEAT.

WEAR GLOVES AT ALL TIMES WHEN HANDLING CONTAINERS.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

16.3 Handling and Disposal

Hydroxyurea Capsules USP are a cytotoxic drug. Follow applicable special handling and disposal procedures *[see References (15)]* .

To decrease the risk of contact, advise caregivers to wear disposable gloves when handling Hydroxyurea Capsules USP or bottles containing Hydroxyurea Capsules USP. Wash hands with soap and water before and after contact with the bottle or capsules when handling Hydroxyurea Capsules USP. Do not open Hydroxyurea Capsules USP. Avoid exposure to crushed or opened capsules. If contact with crushed or opened capsules occurs on the skin, wash affected area immediately and thoroughly with soap and water. If contact with crushed or opened capsules occurs on the eye(s), the affected area should be flushed thoroughly with water or isotonic eyewash designated for that purpose for at least 15 minutes. If the powder from the capsule is spilled, immediately wipe it up with a damp disposable towel and discard in a closed container, such as a plastic bag; as should the empty capsules. The spill areas should then be cleaned three times using a detergent solution followed by clean water. Keep the medication away from children and pets. Contact your doctor for instructions on how to dispose of outdated capsules.

17 PATIENT COUNSELING INFORMATION

- There is a risk of myelosuppression. Monitoring blood counts weekly throughout the duration of therapy should be emphasized to patients taking hydroxyurea *[see Warnings and Precautions (5.1)]* . Advise patients to report signs and symptoms of infection or bleeding immediately.
- Advise patients that there is a risk of cutaneous vasculitic toxicities and secondary malignancies including leukemia and skin cancers *[see Warnings and Precautions (5.2, 5.4)]* .
- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Advise females and males of reproductive potential to use contraception during and after treatment with hydroxyurea capsules *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]* .
- Advise patients to inform their healthcare provider if they have received or are planning to receive vaccinations while taking hydroxyurea capsules as this may result in a severe infection *[see Warnings and Precautions (5.5)]*.
- Advise females to discontinue breastfeeding during treatment with hydroxyurea capsules *[see Use in Specific Populations (8.3)]* .
- Patients with HIV infection should contact their physician for signs and symptoms of pancreatitis, hepatic events, and peripheral neuropathy *[see Warnings and Precautions (5.6)]* .
- Post-irradiation erythema can occur in patients who have received previous irradiation therapy *[see Warnings and Precautions (5.7)]* .

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 01/18
AV Rev. 04/19 (P)

Package/Label Display Panel

AvKARE ®

NDC 42291-321-01

Hydroxyurea
Capsules, USP

Caution: Cytotoxic,
Special Handling Procedures

500 mg

100 Capsules Rx Only

Each capsule contains 500 mg hydroxyurea, USP.

Usual Dosage: Intermittent therapy-single doses of 80 mg per kg every third day. Daily regimen - 20 to 30 mg per kg as a single dose. See package insert for full prescribing information.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

STORE IN A DRY ATMOSPHERE AND AVOID EXCESSIVE HEAT.

WEAR GLOVES AT ALL TIMES WHEN HANDLING CONTAINERS.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured for: **AvKARE, Inc.**
Pulaski, TN 38478

HYDROXYUREA

hydroxyurea capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42291-321(NDC:0555-0882)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HYDROXYUREA (UNII: X6Q56QN5QC) (HYDROXYUREA - UNII:X6Q56QN5QC)	HYDROXYUREA	500 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
SHELLAC (UNII: 46N107B71O)	

PROPYLPARABEN SODIUM (UNII: 625NNB0G9N)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SODIUM PROPIONATE (UNII: DK6Y9P42IN)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
BUTYLPARABEN (UNII: 3QPI1U3FV8)	
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
SODIUM PHOSPHATE, DIBASIC (UNII: GR686LBA74)	
EDETATE CALCIUM DISODIUM (UNII: 25IH6R4SGF)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics

Color	purple, pink	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	barr;882
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-321-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	07/23/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075143	07/23/2013	

Labeler - AvKARE, Inc. (796560394)

Revised: 5/2019 AvKARE, Inc.